H. pylori in the Arctic
Lessons from Community-driven Research

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Canadian North Helicobacter pylori (CANHelp) Working Group
Presentation Objectives

- Understand the challenges of *H. pylori* infection and limitations of available evidence for effective prevention, control and clinical management in northern Canada.

- Understand the need to generate local evidence for effective clinical management of *H. pylori* infection.

- Understand the role of community-driven approaches for creating evidence for public health and clinical interventions.
Presentation Overview

- Brief review of *H. pylori* infection and related disease
- Overview of CANHelp Working Group
- Available evidence on *H. pylori*-related disease burden in Northern Canada
- Highlights from new clinical guidelines and recommendations
- Value of local evidence for effective clinical management
- Value of community-driven approaches to generating local evidence
**Helicobacter pylori**

- A bacterium that colonizes the stomach lining, where it causes inflammation
- Most often acquired during childhood
- Can persist long-term, but can also resolve spontaneously
- Likely spreads most frequently through direct person-to-person contact
  - Probably sheds most often during acute gastroenteritis
  - Evidence neither implicates nor rules out environmental reservoirs
Disease Caused by Helicobacter pylori

- In most chronic cases: only asymptomatic mild gastritis
- In a small fraction of cases (maybe): dyspepsia
  - Large meta-analyses estimate ~7% of dyspeptic people with \( H. \text{ pylori} \) infection have symptom improvement after treatment (Chey WD, et al, ACG Guideline. *Am J Gastroenterol* 2017; 112: 212–23)
  - We don’t know how this estimate varies across populations
- In a small fraction of chronic cases:
  - Peptic ulcers (~10%)*
  - Stomach cancer (~1%)*
    *(very rough estimates of lifetime risk)*
CANHelp Working Group

**CANHelp: Canadian North *Helicobacter pylori***

- Arose from a research collaboration that formed in 2006 in response to:
  - Communities concerned about health risks from *H. pylori* infection
  - Health care providers seeking information to improve clinical management of *H. pylori* infection
  - Public health officials wanting evidence to inform health policy related to *H. pylori* infection
Stomach Cancer in Indigenous Populations

- Higher burden of stomach cancer in Indigenous populations globally (Arnold et al., 2014)

- Circumpolar Inuit: age standardized incidence of stomach cancer was higher than the global average (1989-2008?) (Young et al 2016)
Little Data on *H. pylori*-related Disease in Indigenous Arctic Canadians

- **Peptic Ulcer Disease**
  - Increased ratio of gastric ulcer to duodenal ulcer – *a pattern consistent with increased risk of gastric cancer*
    - Inuit of northern Labrador (*William 1985*)
    - Also observed in studies of
      - Alaska Natives (*Thompson 1975; Sacco 2007*)
      - Native Greenlanders (*Ingeman-Nielsen 1990*)
      - Residents of Arctic Norway (*Eriksen 1995*)
Little Data on *H. pylori*-related Disease in Indigenous Arctic Canadians

**Stomach Cancer**

- **NWT (1993-2000) (Data from NWT Health and Social Services, 2003 and 2014)**
  - 2.9 (95% CI 1.3-5.5) times the incidence rate of all men in Canada
  - In Dene First Nations men, 3rd most common cancer (tied with prostate) at 7% of cancers diagnosed; 10% of cancer deaths
  - In Inuit men, 2nd (after lung) at 16% of cancers diagnosed

- **NWT and Yukon (2003-2007)**
  - Of the total 28 stomach cancer cases, 13 were diagnosed in people under 60 years of age.

- **Inuit Nunangat (1998-2007) [Labrador, Quebec, Nunavut, NWT]**
  - Incidence rates were estimated to be 1.6x and 1.5x the Canadian rates for males and females, respectively (*Carriere et al.*, 2012)
Little Data on *H. pylori*-related Disease in Indigenous Arctic Canadians

- **Stomach Cancer**
  - Because populations are small, we lack accurate information about current rates, trends over time and who is most at risk
Study of multiple southern provinces:

- 30%
- 51%
- 95%
- 35%
- 38%

$H.\text{ pylori}$ infection in Canada
### Project Participation

<table>
<thead>
<tr>
<th>Community Projects</th>
<th>Launch Year</th>
<th>Participants</th>
<th>Breath Tests</th>
<th>Endoscopy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aklavik (Population ~590)</td>
<td>2007</td>
<td>376</td>
<td>333</td>
<td>195</td>
</tr>
<tr>
<td>Old Crow (Population ~250)</td>
<td>2010</td>
<td>208</td>
<td>200</td>
<td>65</td>
</tr>
<tr>
<td>Tuktoyaktuk (Population ~900)</td>
<td>2011</td>
<td>108</td>
<td>105</td>
<td>13</td>
</tr>
<tr>
<td>Fort McPherson (Population ~800)</td>
<td>2012</td>
<td>236</td>
<td>228</td>
<td>57</td>
</tr>
<tr>
<td>Ross River (Population ~350)</td>
<td>2016</td>
<td>89</td>
<td>86</td>
<td>-</td>
</tr>
<tr>
<td>Teslin (Population ~350)</td>
<td>2016</td>
<td>106</td>
<td>105</td>
<td>-</td>
</tr>
<tr>
<td>Inuvik (Population ~3,500)</td>
<td>2017</td>
<td>50</td>
<td>50</td>
<td>-</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td><strong>1173</strong></td>
<td><strong>1107</strong></td>
<td><strong>330</strong></td>
</tr>
</tbody>
</table>
**H. pylori Infection Prevalence in Community Project Participants**

<table>
<thead>
<tr>
<th>Community project</th>
<th>H. pylori prevalence by UBT</th>
<th>Number with results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aklavik, NT</td>
<td>58</td>
<td>332</td>
</tr>
<tr>
<td>Old Crow, YT</td>
<td>66</td>
<td>194</td>
</tr>
<tr>
<td>Tuktoyaktuk, NT</td>
<td>57</td>
<td>103</td>
</tr>
<tr>
<td>Ft. McPherson, NT</td>
<td>59</td>
<td>209</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>60</strong></td>
<td><strong>838</strong></td>
</tr>
</tbody>
</table>
### Prevalence of Endoscopic Diagnoses

**among 324 participants who had upper GI endoscopy**

<table>
<thead>
<tr>
<th>Disease</th>
<th>n</th>
<th>% of 324</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastritis</td>
<td>44</td>
<td>14</td>
</tr>
<tr>
<td>Gastric Erosions</td>
<td>22</td>
<td>7</td>
</tr>
<tr>
<td>Gastric Ulcer</td>
<td>9</td>
<td>3</td>
</tr>
<tr>
<td>Duodenitis</td>
<td>19</td>
<td>6</td>
</tr>
<tr>
<td>Duodenal Erosions</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Duodenal Ulcer</td>
<td>3</td>
<td>1</td>
</tr>
</tbody>
</table>

**Highlights:**
- 3:1 ratio, gastric:duodenal ulcer
- More frequent gastric than duodenal disease

*Pattern consistent with increased risk of gastric cancer*
**Prevalence of Pathological Diagnoses by H. pylori (HP) status among 323 participants with gastric biopsies**

<table>
<thead>
<tr>
<th></th>
<th>Arctic Residents</th>
<th></th>
<th>Edmonton Patients</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HP+</td>
<td>HP-</td>
<td>HP+</td>
<td></td>
</tr>
<tr>
<td><strong>n</strong></td>
<td>% of 231</td>
<td>% of 92</td>
<td>%*</td>
<td></td>
</tr>
<tr>
<td>Chronic Gastritis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>110</td>
<td>48</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Moderate</td>
<td>102</td>
<td>44</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Mild</td>
<td>17</td>
<td>7</td>
<td>13</td>
<td>14</td>
</tr>
<tr>
<td>None</td>
<td>2</td>
<td>1</td>
<td>78</td>
<td>85</td>
</tr>
<tr>
<td>Atrophy</td>
<td>100</td>
<td>43</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Intestinal</td>
<td>41</td>
<td>18</td>
<td>5</td>
<td>5</td>
</tr>
</tbody>
</table>

Highlights:
- Severe gastritis and atrophy limited to HP+ group
- High prevalence of severe gastritis and gastric atrophy in HP+ group relative to other HP+ populations

*Pattern consistent with increased risk of gastric cancer*

*n=282 for gastritis severity
*n=401 for atrophy and metaplasia*
“A decade ago it seemed that *Helicobacter pylori* treatments would soon...provide the same high level of treatment success demanded of other common infections. Unfortunately, that goal was not achieved and...the effectiveness of most commonly recommended treatments has declined to unacceptably low levels, largely related to development of resistance to clarithromycin.

“There are many reasons that successful treatment...of *H pylori* infections remains a challenge. These reasons include...the nature of the organism itself,...the intragastric environment where the organism resides...the regimens used to eradicate the organism...and the behaviour and reactions of the host.
“Clinicians should use the rule ‘only use what works locally’ and should ignore consensus statements and society guidelines if the results are not consistent with local treatment results.”
“Because *H pylori* is typically acquired in childhood, most patients have been infected for many decades and clinicians should feel no sense of urgency regarding initiating treatment. Physicians should take whatever time is needed to gather the information needed for a successful result.”
New Clinical Guidelines and Recommendations

Published guidelines that cite CANHelp community project results

- 2016 Arctic Regions Expert Commentary – 2016
  *Epidemiol Infect* 2016, 144, 225–233
- 2016 Toronto Consensus
  *Gastroenterology* 2016, 151:1, 51-69
- 2016 Alberta Clinical Practice Guidelines (based on Toronto Consensus)
- 2017 AGC Practice Guideline – Management of *H. pylori* Infection
  *Am J Gastroenterol* 2017 advanced online publication doi: 10.1038/ajg.2016.563

Guidelines that CANHelp academic researchers co-authored

- 2016 Arctic Regions Expert Commentary – 2016 (Goodman)
- 2016 Toronto Consensus (van Zanten)
- 2016 Alberta Clinical Practice Guidelines (van Zanten)
- 2017 NASPGHAN-ESPHGHAN Pediatric Guidelines – update forthcoming (Goodman)
  *J Pediatr Gastroentrol Nut*, in press
New Clinical Guidelines and Recommendations

- **New directions common to new guidelines**
  - Greater caution about “test and treat”
  - Greater caution about clarithromycin-based triple therapy
  - Longer duration of recommended regimens (14 days)
  - Emphasis on importance of confirming treatment success
New Clinical Guidelines and Recommendations

❖ New directions common to new guidelines
  ➤ Greater caution about “test and treat”
    ➤ Test and treat patients with
      ➤ Confirmed peptic ulcer disease
      ➤ (MALT) lymphoma or endoscopic resection of early gastric cancer
    ➤ Endoscopy indicated for
      ➤ New onset dyspepsia in adults >50
      ➤ Dyspepsia in younger adults with
        • Poor response to acid-suppression treatment
        • Alarm symptoms: vomiting, bleeding/anemia, abdominal mass, unexpected weight loss, dysphagia

Note: who to test and who to treat are the same because testing should not be done unless treatment will be offered.
New Clinical Guidelines and Recommendations

- **New directions common to new guidelines**
  - Greater caution about “test and treat”
    - *Consider* non-invasive test and treat for patients with dyspepsia only if:
      - No alarm symptoms
      - <50 years old
  - Help patients understand that treatment may not cure symptoms
  - Consider the patient’s
    - Preferences in weighing pros and cons of treatment
      - Reducing risks from *H. pylori* infection, adverse effects of antibiotics
    - Ability to tolerate and adhere to treatment regimen
    - Family history of *H. pylori* infection, peptic ulcer disease and gastric cancer
    - Probability of reinfection (based on relevant data)
New Clinical Guidelines and Recommendations

- New directions common to new guidelines
  - Greater caution about clarithromycin-based triple therapy
    - Use as first-line regimen only if resistance to clarithromycin is unlikely, based on
      - Susceptibility testing, if available
      - Local prevalence of resistance, if known
      - Patient’s past exposure to clarithromycin
    - Where clarithromycin resistance is likely or treatment failure is common, bismuth-based quadruple therapy is preferred
New Clinical Guidelines and Recommendations

- New directions common to new guidelines
  - Longer duration of recommended regimens (e.g., 14 days)
    - Can overcome some degree of resistance
    - Can help prevent greater resistance from developing
    - Especially important where treatment failure is common
New Clinical Guidelines and Recommendations

- New directions common to new guidelines
  - Emphasis on importance of confirming treatment success
    - Provides local information on treatment effectiveness
    - Identifies patients who need another course of treatment
      - In such cases, a different regimen should be used
What about screening people for *H. pylori* for research?

- Some people feel alarmed when they find out they tested positive for *H. pylori*
- To minimize the alarm, we use careful messaging; when we inform participants they had a positive breath-test result, we tell them the following
  - Most people with *H. pylori* infection have had the infection for most of their life and do not need to get treated right away
  - For most CANHelp project participants it is ok to wait until plans are in place for community-wide treatment
  - If you do not feel well, you should seek care at your regular place of care
  - If you are worried about your test result, you can speak to our specialist stomach doctor (gastroenterologist)
  - Waiting for community-wide treatment through the CANHelp project offers the opportunity to have a scope test through the project and to receive treatment when project staff are in a better position to support you during treatment
### Community Project Treatment Trial
Results to Date

<table>
<thead>
<tr>
<th></th>
<th>% Successfully Treated (95% CI)</th>
<th>n (number treated)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Triple</td>
<td>Sequential</td>
</tr>
<tr>
<td>All participants</td>
<td>62 (48-74)</td>
<td>71 (61-79)</td>
</tr>
<tr>
<td></td>
<td>n=58</td>
<td>n=99</td>
</tr>
<tr>
<td>Participants in treatment trial (randomized to regimen)</td>
<td>62 (46-75)</td>
<td>73 (63-82)</td>
</tr>
<tr>
<td></td>
<td>n=47</td>
<td>n=89</td>
</tr>
</tbody>
</table>

CI, confidence interval

*Treatment success confirmed by UBT >10 weeks post treatment*
Preliminary Community Project Follow-up Results

- UBT results for participants aged 18-80 after a mean follow-up of 3 years
  - Among 38 who were initially negative, 33 (87%) remained negative
  - Among 43 who were negative after treatment, 41 (95%) remained negative

- Estimated re-infection proportion during the follow-up period:
  4.7% (95% CI: 0.6-16.0%)

- Combined re-infection/incidence rate in 72 Indigenous participants
  2.4% per year (95% CI: 0.8-5.9% per year)

- The following groups remained free from infection
  - All 9 non-Indigenous participants
  - All 23 participants aged 55 and older

Why do we need new approaches?

- Effective primary prevention measures have not been identified
- Vaccines are not yet available
- Large trials show that the elimination of *H. pylori* infection in adults reduces gastric cancer rates
Why do we need new approaches?

A body of literature shows that screening for and treating *H. pylori* infection would be cost-effective for preventing gastric cancer under a wide range of scenarios, but prevention measures have not been implemented, outside of a few trials, because it is not yet clear who to target or how to screen and treat.

Prevention strategies should be tailored to the local context because of variation in:

- Available resources
- Sociocultural priorities
- Intervention costs
- Intervention effectiveness:
  - Screening accuracy
  - Treatment effectiveness
Why do we need new approaches?

- Integration of preventive services across clinical and public health sectors is needed because:
  - Health is affected by multiple levels of influence including individuals, families, larger groups, populations and ecosystems
  - Disease prevention initiatives can be more effective when they expand opportunities for prevention through partnerships across health systems, communities, academia, business, and the media
Value of local evidence

- The effectiveness of interventions depends on the context
  - Implementing clinical management strategies without considering local evidence may reduce the effectiveness of the strategies

- Local evidence is readily actionable
  - For example, years before evidence generated by our community projects was included in reviews and clinical guidelines, it had already informed changes to prescribing practices in the Beaufort-Delta region of the NWT

- Local evidence is accepted
  - It was not difficult for us to impact clinical practice in the region, because the public health physicians who set the policy knew how the evidence was produced and valued it
Value of community-driven methods

- **Community-engaged research can**
  - Be part of a multilevel approach to develop and implement effective prevention strategies
  - Build relationships between community members and healthcare providers
    - Collaborative research that responds to community concerns demonstrates to community members that healthcare providers and academic researchers value their perspectives and are willing to work together to find solutions
  - Build capacity in communities
    - Community members can develop skills for contributing to the development of local evidence in the future
    - Local care providers can develop research skills for generating local evidence in a clinical setting
Acknowledgements

- Alberta Innovates – Health Solutions (AIHS)
- Canadian Institutes for Health Research (CIHR)
  - Institute of Aboriginal People’s Health
  - Network Environment for Aboriginal Health Research (NEAHR)
    - Anisabe Kekendazone, Ottawa
    - Nasivvik
- ArcticNet Network of Centres of Excellence of Canada
- Indigenous and Northern Affairs Canada
- Ualberta North
Higher burden of stomach cancer in Indigenous populations globally \textit{(Arnold et al., 2014)}

- Age-adjusted Incidence Rate Ratios
  - Sami people, Sweden, 1961-2003
    - 1.23x (males) and 1.53x (females) the rates of non-Sami \textit{(Young et al., 2016)}
  - Maori people, New Zealand, 2003-2007
    - 2.6x (males) and 3.8x (females) the rates of non-Maori \textit{(Moore et al., 2015)}
    - 3.0x (both sexes) the rates of white Alaskans \textit{(Moore et al., 2015)}
Gastric Cancer in Indigenous Populations (North)

- Circumpolar Inuit

1989-2008

- Stomach cancer, age-standardized incidence rates:
  - Males: 27.7 per 100,000
  - Females: 11.1 per 100,000

Cancer incidence relative to the GLOBOCAN world average by site (1989-2008?) (Young et al 2016)
Little Data on *H. pylori*-related Disease in Indigenous Arctic Canadians

**Gastric Cancer**

*(Data from Cancer in the Northwest Territories. NWT Health and Social Services, 2003 and 2014)*

- **Northwest Territories**
  - **1993-2000**
    - 9 cases among all men in regional centres
      - 2.9 (95% CI, 1.3, 5.5) times the incidence rate of all men in Canada
    - In Dene First Nations men, 3rd most common cancer (tied with prostate) at 7% of cancers diagnosed; 10% of cancer deaths
    - In Inuit men, 2nd (after lung) at 16% of cancers diagnosed
  - **2001-2010**
    - 11 cases of stomach cancer among all females (2.0% of total cases) – *published data*
    - 13 cases observed in males over this time period (2.3% of total cases) – *partner communication*
Little Data on *H. pylori*‐related Disease in Indigenous Arctic Canadians

**Gastric Cancer**

- **Northwest Territories (NWT) and Yukon (YT)**
  - **2003-2007**
  - New cases of stomach cancer and age-standardized incidence rates (ASIR), all ethnic groups

<table>
<thead>
<tr>
<th>Area</th>
<th>Males Cases</th>
<th>ASIR (95%CI)</th>
<th>Females Cases</th>
<th>ASIR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canada</td>
<td>9,640</td>
<td>11.1 (10.8, 11.3)</td>
<td>5,401</td>
<td>4.9 (4.7, 5.0)</td>
</tr>
<tr>
<td>NWT &amp; YT</td>
<td>15</td>
<td>11.5 (5.0, 18.0)</td>
<td>13</td>
<td>9.7 (4.0, 15.5)</td>
</tr>
</tbody>
</table>

Note: rate per 100,000; standardized to the Canadian 1991 population

Source: International Agency for Research on Cancer, CISX

- Of the total 28 stomach cancer cases, 13 were diagnosed in people under 60 years of age.
Little Data on *H. pylori*-related Disease in Indigenous Arctic Canadians

- Gastric Cancer
  - Inuit Nunangat
    - 1998-2007
  - Incidence rates were estimated to be 1.6x and 1.5x the Canadian rates for males and females, respectively *(Carriere et al., 2012)*